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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
08/14/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	09/461,090	ULLRICH ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-45,47 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-45,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on June 4, 2007 has been entered. The claims pending in this application are claims 40-45, 47, and 48. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the response filed on June 4, 2007.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 40-43, 45, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claims 45 and 47 have a limitation "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor". First, although page 2, lines 5-22 of the specification describes that the activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, the specification fails to define or provide any disclosure to support such claim limitation. Although original claim 1 contains the language "G protein mediated signal transduction" and original claim 3 contains "an

extracellular signal pathway", and page 2, lines 7-10 of the specification describes that activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, these descriptions only supports that growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction. Furthermore, although the examiner agrees that the exact language used in the claims does not need to appear in the specification, since the phrase "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" is not limit to "growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction" and is much broader than the disclosure in the specification, the phrase "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" recited in claims 45 and 47 is a new matter. Second, although page 3, line 15 of the specification suggested by applicant describes CRM197, a catalytically inactive form of the diphtheria toxin, which specifically binds to proHB-EGF and which is capable of blocking the processing of proHB-EGF by metalloproteinase, since it is known that EGF is released from its precursor by metalloproteinase and EGFR is activated by EGF, CRM197 cannot serves "a compound which directly acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" as recited in claims 45 and 47. Therefore, page 3, line 15 of the specification does not support the phrase "a compound which directly acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" as recited in claims 45 and 47. Third, although the specification describes "the present invention provides methods for preventing or treating, among other diseases, hyperproliferative diseases such as colon, pancreatic, prostate, gastric, breast, lung, thyroid, pituitary, adrenal and ovarian

tumors, as well as thyroid hyperplasia, retinitis pigmentosa, precocious puberty, acromegaly and asthma. More particulary, the growth of human prostate cancer cells may be inhibited by treatment with proteinase inhibitors such as batimastat" (see page 3, third paragraph), the specification does not support to *in vitro* methods recited in claims 44 and 45 wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells. Therefore, the phrase "wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cell" recited in claims 44 and 45 is a new matter.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application". MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

Response to Arguments

In page 6, second paragraph bridging of applicant's remarks, applicant argues "[T]he claims have been amended to indicate that the present invention 'modulates growth factor receptor activation by modulating G-protein mediated signal transduction'. In view of this amendment, applicants request that this rejection be withdrawn. Regarding the language 'a compound which directly acts on a growth factor precursor', this language is supported by the disclosure on page 3, line 15). This disclosure shows a specific compound which directly binds

to a growth factor precursor. In view of the above amendments, applicants request that this rejection be withdrawn".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Although page 2, lines 5-22 of the specification describes that the activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, the specification fails to define or provide any disclosure to support such claim limitation. Although original claim 1 contains the language "G protein mediated signal transduction" and original claim 3 contains "an extracellular signal pathway", and page 2, lines 7-10 of the specification describes that activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, these descriptions only supports that growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction. Furthermore, although the examiner agrees that the exact language used in the claims does not need to appear in the specification, since the phrase "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" is not limit to "growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction" and is much broader than the disclosure in the specification, the phrase "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" recited in claims 45 and 47 is a new matter. In addition, although page 3, line 15 of the specification suggested by applicant describes CRM197, a catalytically inactive form of the diphtheria toxin, which specifically binds to proHB-EGF and which is capable of blocking the processing of proHB-EGF by metalloproteinase, since it is known that EGF is released from its precursor by metalloproteinase and EGFR is activated by EGF, CRM197 cannot serves "a

compound which directly acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" as recited in claims 45 and 47. Therefore, page 3, line 15 of the specification does not support the phrase "a compound which directly acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" as recited in claims 45 and 47.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 40-45, 47, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 44 is rejected as vague and indefinite. Although claim 44 is directed to a method for identifying a test compound for modulating a G-protein mediated signal transduction, from the method steps in the claim, it is unclear that, in which situation, the test compound can be considered as a compound that has an ability to modulate a G-protein mediated signal transduction. Please clarify.

7. Claim 45 or 47 is rejected as vague and indefinite. Although claim 45 or 47 is directed to a method for modulating growth factor receptor activation by modulating a G-protein mediated signal transduction, from the method steps in the claim, it is unclear how to modulate the receptor tyrosine kinase activation by G-protein mediated signal transduction. Please clarify.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dong *et al.*, (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999) in view of Klemke *et al.*, (The Journal of Cell Biology, 127, 859-866, 1994).

Dong *et al.*, teach metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor.

Regarding claim 44, Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see canceled claim 36 of this instant application) and Dong *et al.*, teach that batimastat decreases level of EGFR tyrosine phosphorylation in the HMEC cells (see page 6238, right column and Figure 4), Dong *et al.*, disclose contacting a cell containing a receptor tyrosine kinase (ie., a HMEC cell) capable of activation by G-protein mediated signal transduction with a test compound (ie., batimastat) as recited in the claim. Since Dong *et al.*, teach that batimastat is a selective metalloprotease inhibitor that prevents EGFR ligand release (see page 6235, abstract and right column, and page 6239, right column, last paragraph) and there is no evidence to show that batimastat can not

affect a G protein or G protein coupled receptor initiated extracellular signal pathway, Dong *et al.*, disclose a test compound (ie., batimastat) suspected to indirectly act on a ligand precursor of the receptor tyrosine kinase (ie., EGFR, by preventing EGFR ligand release) as recited in the claim. Since Dong *et al.*, teach to compare the level of EGFR tyrosine phosphorylation of the HMEC in the presence of batimastat, antagonist mAb225 or EGF (see Figure 4), Dong *et al.*, disclose evaluating G-protein mediated receptor tyrosine kinase (ie., EGFR) activation upon exposure of the cell (ie., the HMEC cells) to said test compound (ie., batimastat) as an indication of said test compound's ability (ie., with or without ability) to modulate G-protein mediated signal transduction thereby identifying a test compound for modulating G-protein mediated signal transduction as recited in the claim.

Regarding claim 45, since Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4) and teach that ligands such as EGF that activate the epidermal growth factor receptor (EGFR) are synthesized as membrane-anchored precursors that are proteolytically released by members of the ADAM family of metalloproteases and batimastat is a metalloproteinase inhibitor that prevents EGFR ligand such as EGF release by abolish biological activity of the metalloproteinases (see page 6235, abstract and right column, and page 6239, right column, last paragraph), and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway and claim 45 does not require that stimulating step must be performed before contacting step, Dong *et al.*, disclose contacting a cell with a compound (ie., batimastat) which indirectly acts on a growth factor precursor (by preventing EGFR ligand such as EGF release) in a G protein mediated

extracellular signal pathway as recited in claim 45. Since Dong *et al.*, teach that the inhibitory effect of batimastat on EGFR tyrosine phosphorylation of the HMEC cells is totally reversed by EGF (see Figure 4, column 5 in the presence of batimastat +EGF), batimastat has no effect on EGFR tyrosine phosphorylation of HMEC cells in the presence of EGF, comparing with batimastat treated HMEC cells, the HMEC cells treated with batimastat +EGF has an increased level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see canceled claim 36 of this instant application), Dong *et al.*, disclose stimulating G protein mediated signal transduction in a cell (ie., treating the HMEC cells with batimastat+EGF) having a receptor tyrosine kinase (ie., EGFR) wherein the receptor tyrosine kinase is activated and thereby modulating the receptor tyrosine kinase activation by G-protein-mediated signal transduction (ie., increasing the level of EGFR tyrosine phosphorylation) wherein said tyrosine kinase is EGFR as recited in claim 45. Since it is known that EGFR has an extracellular domain and a cell comprising EGFR has a G-protein mediated signal transduction pathway wherein EGFR activation occurs by tyrosine phosphorylation of EGFR (see the specification, page 1, last paragraph, and page 2, second paragraph), Dong *et al.*, disclose that said receptor tyrosine kinase is EGFR and said cell (ie., the HMEC cell) comprising the extracellular domain of EGFR and having a G-protein mediated signal transduction pathway wherein one or more tyrosine residues are phosphorylated based on the activation of said G-protein mediated signal transduction pathway as recited in claim 45. Since Dong *et al.*, teach that EGF is generated from its membrane-anchored precursor by one of the ADAM family of

metalloproteases (see page 6235, abstract) and it is know that EGF binds to the extracellular domain of EGFR, Dong *et al.,* disclose that the extracellular domain of said receptor (ie., EGFR) is capable of binding to its receptor ligand (ie., EGF) and said ligand is generated from a precursor of said ligand (ie., the precursor of EGF) by a proteinase-dependent cleavage (ie., one of the ADAM family of metalloproteases) thereby modulating the receptor tyrosine kinase activation by G-protein mediated signal transduction as recited in claim 45.

Dong *et al.,* do not disclose to perform the methods recited in claims 44 and 45 using a cancer cell wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cell.

Klemke *et al.,* teach a human pancreatic carcinoma cell containing EGFR (see abstract in page 859).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 44 and 45 wherein said cancer cell is pancreatic tumor cell in view of the references of Dong *et al.,* and Klemke *et al...* One having ordinary skill in the art would have been motivated to do so because the simple replacement of one kind of cell line having EGFR (ie., a human mammary epithelial cell line taught by Dong *et al.,*) from another kind of cell line having EGFR (ie., a human pancreatic carcinoma cell containing EGFR taught by Klemke *et al.,*) during the process of performing the method recited in claims 44 and 45 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since both the human mammary epithelial cell line taught by

Dong *et al.*, and the human pancreatic carcinoma cell taught by Klemke *et al.*, contain EGFR and are used for the same purpose (ie., measuring phosphorylation of EGFR).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. No claim is allowed.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

August 3, 2007

FRANK LU
PRIMARY EXAMINER